

REMARKS

Applicants have carefully considered this Application in connection with the Examiner's Action, and respectfully request reconsideration of this Application in view of the above amendments and the following remarks.

Claims 5, 6, and 8-15 are pending in this application.

Claim 8 has been amended to correct a typographical error resulting in an improper claim dependency.

I. EXAMINER'S RESPONSE TO ARGUMENTS – CLAIM OBJECTIONS

Applicants wish to thank the Examiner for withdrawing the objections to Claim 9 and Claim 15.

II. CLAIM REJECTIONS UNDER 35 USC §103

The Examiner has maintained the rejection of Claims 5-6 and 8-15 under 35 U.S.C. 103(a) as being unpatentable over Drewett et al. (Journal of Biological Chemistry [2001] 276:36, 33444-33451, "the Drewett Reference") in view of Narula et al. (PNAS [1999] Vol. 96, 8144-8149, "the Narula Reference").

The Examiner states that it would have been obvious to one of skill in the art at the time the invention was made to combine the teachings of the Drewett Reference with the Narula Reference to develop a method of diagnosing cardiac disease in an individual comprising the step of identifying cleavage of SRF in at least one cell from a sample from said individual and that the Narula Reference indicates the relationship between apoptosis and heart failure, while the Drewett Reference describes the relationship between Serum Response Factor (SRF) cleavage and apoptosis.

Applicants respectfully disagree. Although it may seem clear to one familiar with the specification of the current application, it would not have been evident in the absence of the current disclosure that specific cleavage fragments from caspase-3 cleavage of SRF would be associated with human heart failure. There is no basis for combining the elements from these separate references to arrive at the claimed material, and to combine the references constitutes impermissible hindsight picking and choosing on the part of the Examiner. Therefore, to hold that the currently claimed material is not novel or is obvious is not proper as held by the Court:

“An obvious-to-experiment standard is not an acceptable alternative for obviousness. Selective hindsight is no more applicable to the design of experiments than it is to the combination of the prior-art teachings.”

In re Dow Chemical Co., 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988)

The Narula Reference is silent with regard to measuring cleaved SRF in human hearts to diagnose cardiac disease in an individual. The Examiner then relied upon the teaching of the Drewett Reference to “fill in the gap” of measuring cleaved SRF. In order to arrive at the claimed material, the Examiner is selectively choosing the disclosure in the Drewett Reference, but ignoring other teachings which would have led one of skill to believe that fragments of SRF associated with cardiac disease were spliced and not cleaved. For example, Davis et al., 2002 (previously cited), which recites “(t)hese results suggest that expression of SRF-Δ4,5 in failing hearts may in part contribute to impaired cardiac gene expression and consequently to the pathogenesis of heart failure” (see abstract).

Moreover, it would not have been clear to one of skill in the art that the specific regions of SRF disclosed in the current application would have been useful in the accurate measurement of cleaved SRF for this purpose. The references do not teach the measurement of an N-terminal or C-terminal region of SRF or SEQ ID NO:5.

In contrast, the present invention describes directly a method of diagnosing cardiac disease in an individual by measuring cleavage of SRF in a cardiac cell from the individual. The measurement of any particular biomarker is an unpredictable and sensitive technique, and biomarker pathways are complex and interwoven. Just because a particular protein is activated under one set of conditions in an *in vitro* experiment, does not mean that it will show a similar profile in a human heart *in vivo*. Extensive experimentation would have been required to develop the currently claimed material based on the cited references.

The Drewett Reference describes experiments in the Burkitt’s lymphoma cell line, BJAB. The results and conclusions of the Drewett Reference are derived from the behavior in this cancer cell line. There are obviously enormous differences in biology, physiology, and biochemistry between a human cardiomyocyte and a lymphoma cancer cell line. Observations in BJAB cells do not automatically or logically lead to the same conclusion in a heart cell. At best, evidence from these cells could be considered obvious to try.

With regard to the Narula Reference, there is a similar lack of motivation to combine the references. Apoptosis has been observed in failing human hearts according to this paper, however, given the fact that there are many proteins which are targets for caspase cleavage, the conclusion that apoptosis occurs in failing human hearts does not provide any implication of SRF as one of the caspase cleavage targets.

Furthermore, unexpected results were obtained when the current invention was first discovered. What is understood about the SRF gene itself would lead one of ordinary skill in the art away from the idea that SRF is a caspase 3 cleavage target in the heart. SRF is an ancient gene, and highly conserved among species from fly to human being. It is indispensable for heart development. Because of the pivotal role the gene plays, it would be considered by one of skill in the art to be one of the least likely candidates for caspase cleavage in the heart. In fact, according to the invention, caspase-3 cleavage of SRF does occur in the cardiomyocytes.

A further unexpected result was that the truncated SRF protein maintains biologically activity, and functions as a dominant negative transcription factor (see Example 5, paragraph [0306]). Not only was the amount of SRF cleaved by caspases significantly increased in human failing heart tissues compared to normal hearts, but the cleavage generated a dominant negative transcription factor, which in some embodiments leads to the depression of transcription of cardiac-specific genes. Therefore, it was not only SRF cleavage, but subsequent biological activity of an SRF fragment, which led to drive the heart into failure.

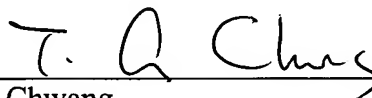
Therefore, there is no teaching or suggestion in the Drewett and Narula References, either alone or in combination which would have led one of skill in the art to develop the currently claimed invention. Further, the results obtained here are totally unexpected as discussed above. Applicants therefore respectfully submit that Claims 5-6 and 8-15 are in condition for allowance.

III. CONCLUSION

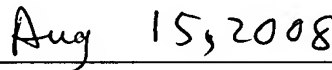
Applicants respectfully submit that, in light of the foregoing Amendment and comments, Claims 5, 6, and 8-15 are in condition for allowance. A Notice of Allowance is therefore requested.

If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,



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